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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/881,535	06/14/2001	Vasulinga T. Ravikumar	ISIS-4785	8150

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WOODCOCK WASHBURN LLP
ONE LIBERTY PLACE - 46TH FLOOR
PHILADELPHIA, PA 19103

EXAMINER

EPPS, JANET L

ART UNIT	PAPER NUMBER
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1635

15

DATE MAILED: 06/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/881,535

Applicant(s)

RAVIKUMAR, VASULINGA T.

Examiner

Janet L. Epps-Ford

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 March 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-40 is/are pending in the application.
- 4a) Of the above claim(s) 17-32 and 37-40 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-16 and 33-36 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 13.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

Art Unit: 1635

DETAILED ACTION

1. The abstract of the disclosure is objected to because the abstract is not a complete sentence. The abstract is not complete since there is no punctuation included in the abstract. Correction is required. See MPEP § 608.01(b).

Response to Arguments

2. Applicant's arguments with respect to claims 1-16 and 33-36 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 1-16 and 33-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cook (US Patent 5,212,295) in view of Barany et al. (US 5,852,168) and Eleuteri et al. (WO-99-664433-A1).

5. The instant claims recite a method for preparing an internucleotide phosphorothioate linkage enriched in the Sp enantiomer between a synthon having a hydroxyl moiety at the 5'-position and a 2'-substituted nucleoside having an activated phosphate moiety at the 3'-position comprising selecting a coupling reagent having a pKa ranging from about 3.3 to about 4.5 and coupling said synthon to said 2'-substituted nucleoside in the presence of said coupling reagent; wherein said coupling reagent is 5-(ethylthio)-1H-tetrazole; wherein said 2'-substituent is O-

Art Unit: 1635

alkyl; and further wherein said activated phosphate moiety comprises a beta-cyanoethyl or an acetoxo phenoxy ethyl group.

Cook teach the synthesis of Sp chirally pure phosphorothioate oligonucleotides comprising reacting an activated nucleoside synthon with a hydroxyl group located on the 5'-phosphate group of a nucleoside attached to a solid support at the 3'-hydroxyl (see for example scheme 1, col. 13-16). The invention of Cook et al. also comprises the use of 2'-O-protected nucleosides in the method for synthesizing chirally pure oligonucleotides. See for example, col. 8 (lines 25-42), wherein the 2' position of the nucleoside synthon (denoted as Rx in structure (1) or RC in structure (4)) comprises an H, hydroxyl, a sugar derivatizing group (see col. 4, line 63), a lower alkyl, O-alkyl, S-alkyl, or substituted O-alkyl or S-alkyl (see col. 6, lines 32-36).

However, the method of Cook et al. does not comprise wherein the coupling agent has a pKa ranging from about 3.3 to about 4.5, wherein said coupling agent is 5-(ethylthio)-1H-tetrazole, or wherein the activated phosphate moiety comprises an acetoxo phenoxy or beta-cyanoethyl phosphate protecting group.

Barany et al. teach the synthesis of phosphorothioates comprising the use of 5-ethylthio-1H-tetrazole as the activator for the coupling of beta-cyanoethyl-ribonucleoside phosphoramidites to a controlled pore glass solid support loaded with the 3'-end of a ribonucleoside residue (the attachment of the 3'-end is indicative that the coupling reaction occurred with the 5' end of the attached ribonucleoside). Barany et al. teach that 5-ethylthio-1H-tetrazole was used since it has greater acidity and solubility in acetonitrile than tetrazole. (see col 18, lines 5-35).

Art Unit: 1635

Eleuteri et al. teach the use of acetoxymethoxy ethyl and beta-cyanoethyl as phosphorus protecting groups useful for protecting phosphorus containing internucleoside linkages during solid state oligonucleotide synthetic regimes (page 9, line 18-21).

It would have been obvious for one of ordinary skill in the art to modify the teachings of Cook et al. with the teachings of Barany et al. to devise a method for synthesizing a phosphorothioate oligonucleotide enriched with the Sp enantiomer comprising the use of 5-ethylthio-1H-tetrazole as the activator for coupling of nucleoside residues in phosphorothioate oligonucleotide synthesis. One of ordinary skill in the art would have been motivated to make this modification because Barany et al. teach that 5-ethylthio-1H-tetrazole is a suitable activator for phosphorothioate synthesis, and it performs the same function as the DBU activator used in the method of Cook et al. It is prima facie obvious for ordinary skilled artisan to substitute one functionally equivalent activator for another in the synthesis of the same class of molecules, in particular phosphorothioate oligonucleotides. Moreover, although Barany makes no mention of the pKa of 5-ethylthio-1H-tetrazole, absent evidence to the contrary, 5-ethylthio-1H-tetrazole inherently possesses a pKa of between 3.3 and 4.5.

Additionally, it would have been obvious for one of ordinary skill in the art at the time of filing to modify the teachings of Cook et al. with the teachings of Eleuteri et al. to produce a method for synthesizing phosphorothioate comprising the use of activated monomers comprising a phosphate moiety that is activated with an acetoxymethoxy ethyl or beta-cyanoethyl protecting group. One of ordinary skill in the art would have been motivated to make this modification in order to prevent unwanted side reactions with the substituents of the phosphate moieties of the individual monomers during the successive coupling reactions, additionally, Eleuteri et al. teach

Art Unit: 1635

that these protecting groups are well suited for protecting phosphorus containing internucleoside linkages during solid state oligonucleotide synthetic regimes.

Therefore the invention as a whole is *prima facie* obvious over Cook et al. in view of Barany et al. and Eleuteri et al.

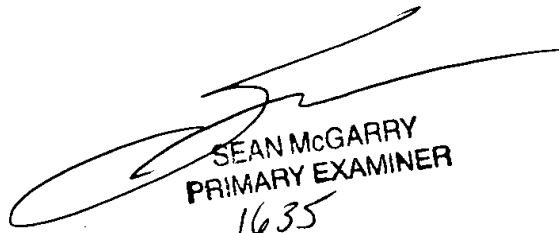
6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Friday 8:30AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE
June 9, 2003


SEAN MCGARRY
PRIMARY EXAMINER
1635